PATENT SPECIFICATION

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765,849

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International Classification:—C07c.

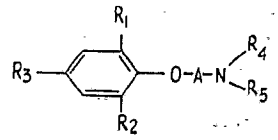
COMPLETE SPECIFICATION

Improvements in or relating to New Aminoalkyl Phenyl Ethers

We, THE UNIVERSITY OF LEEDS, a British Body Corporate, of University Road, Leeds, in the County of York, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

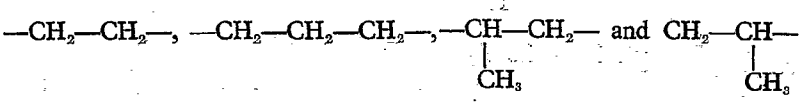
This invention relates to new aminoalkyl phenyl ethers possessing valuable pharmacological properties.

According to the present invention there are provided new aminoalkyl phenyl ethers of the general formula I:—



I

in which R_1 and R_2 are the same or different and are chlorine atoms or alkyl groups and R_3 is a hydrogen atom or, where one or both of R and R_2 are lower alkyl groups, a lower alkyl group, A represents a divalent group selected from

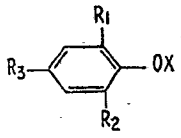


and R_4 and R_5 each represent a lower alkyl group. By the term "alkyl group" is meant an alkyl group containing up to 6 carbon atoms.

These new compounds are of pharmacological value in that they are potent local anæsthetics; compounds of outstanding value in this respect are those in which R_1 and R_2 each represent a methyl group, R_3 represents a hydrogen atom, A represents $—CH_2—CH_2—$ and R_4 and R_5 are the same and represent methyl or ethyl groups; in other words, 2-(β - dimethylaminoethoxy) - 1:3 - dimethylbenzene and 2-(β-diethylaminoethoxy)-1.3-dimethylbenzene.

The new ethers will normally be used in the form of their acid addition salts with acids, such as hydrochloric or hydrobromic acid, which do not give rise to pharmacologically undesirable radicals and it should be understood that where in this specification and in the appended claims reference is made to said ethers it is intended to include such acid addition salts.

According to a feature of the invention, the aforesaid new ethers are prepared by reacting a compound of the general formula II:—

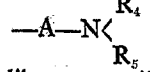


II

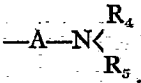
with a compound of the general formula III:—

$$Y—Z \qquad \text{III}$$

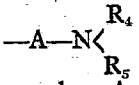
where X, Y and Z represent atoms or atom groups such that X will react with Y—Z to form the tertiary amino grouping



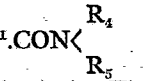
or a group readily convertible into such grouping and, in the latter case, thereafter converting the group obtained into the tertiary amino grouping



Groups which are convertible into the grouping

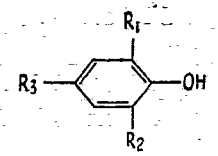


include —A—NH_2 and —A—NHR_4 (both convertible by alkylation), —A.Hlg, where Hlg represents a halogen atom e.g. bromine (convertible by treatment with an amine ) and, applicable in certain cases only,



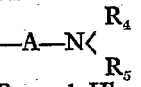
(convertible by reduction). The grouping A^1 represents a grouping differing from a grouping A of the type containing a terminal —CH_2— grouping, only in the omission of the terminal —CH_2— grouping.

A preferred process for preparing the ethers of the present invention comprises reacting the corresponding phenol of the general formula IV:—



IV

(wherein R_1, R_2 and R_3 each have the significance hereinbefore set forth) with a dialkylaminoalkyl halide, preferably the chloride, of the general formula V:—

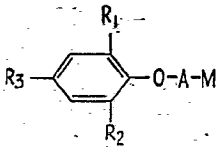


V

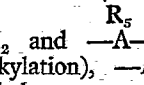
(wherein A, R_4, R_5 and Hlg have the significance hereinbefore set forth), the reaction being preferably effected in the presence of an acid binding agent which may be inorganic in character (for example, potassium carbonate) or organic in character (for example, pyridine or dimethylaniline). The acid binding agent is unnecessary if the phenol is in the form of an alkali metal derivative thereof.

Specific alternative processes for preparing the new ethers of general formula I are as follows:

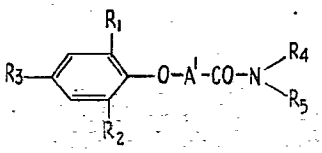
(a) By reaction of an ester of the general formula VI:—



VI

(wherein R_1, R_2 and R_3 each have the significance hereinbefore set forth and M represents an ester radical) with a secondary amine of the type  (wherein R_4 and R_5 each have the significance hereinbefore set forth), the reaction being preferably effected in the presence of an acid binding agent of organic or inorganic character such as pyridine or potassium carbonate.

(b) In the case of compounds in which A represents a grouping containing a terminal —CH_2— grouping attached to the adjacent nitrogen atom, by the reduction of a corresponding amide of the general formula VI:

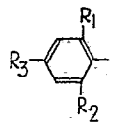


VII

(wherein R_1, R_2, R_3, R_4 and R_5 each have the significance hereinbefore set forth and A^1 is a divalent group differing from A only in the omission of said terminal —CH_2— grouping), the reduction being preferably effected by means of molecular hydrogen in the presence of a precious metal catalyst or by means of chemical reducing agents such as lithium aluminium hydride.

(c) By the alkylation of a corresponding primary amine or of a corresponding secondary amine (containing the substituent R_4) with an alkyl ester of the type R_5M (wherein R_5 and M each have the significance hereinbefore set forth) the reaction being preferably effected in the presence of an acid binding agent in the form of an organic or inorganic base. Where the primary amine is employed, R_4 and R_5 in the final product are, of course, identical.

Those of the starting materials required for the various processes hereinbefore described that are not known substances may be made by the application of methods known for the production of compounds of similar type. (In the following description the symbol Ar denotes the grouping:



and the other symbols referred to are as hereinbefore defined). Thus, for example, primary amines of the type Ar—O—A—NH_2 and secondary amines of the type Ar—O—A—NHR_4 may be produced by reaction of the appropriate ester and phenol, e.g.:

$$Ar.OH + M—A—NHR_4 \longrightarrow Ar—O—A—NHR_4$$

preferably in the presence of an organic or inorganic base; starting materials of the type AR—O—A.NHR_4 are claimed per se in Specification No. 687189; compounds of the type Ar—O—A—M may be prepared by reaction of the appropriate phenol with an appropriate diester, thus:

$$Ar.OH + M—A—M \longrightarrow Ar—O—A—M$$

preferably in the presence of an organic or inorganic base; and compounds of the type $Ar—O—A^1—CONR_4R_5$ may be prepared by reaction of the appropriate phenol with an amide ester of the type $N—A^1—CO.NR_4R_5$.

It will be appreciated that when the grouping A is a branched chain (viz. either $—CH_2CH(CH_3)—$ or $—CH(CH_3).CH_2—$) isomerisation can occur at one stage or another of one of the aforesaid processes with the simultaneous production of both isomers. These two isomers can readily be separated however, by conversion of the ether bases into hydrochlorides, fractional crystallisation from a suitable solvent such as acetone, and if the free ether bases are required, treating the individual isomers thus separated with caustic alkali.

The invention is illustrated by the following Examples.

EXAMPLE I

2:6-Dichlorophenol (27.7 gm; 0.17 mol.) is added to a solution of potassium hydroxide 85% (13 gm; 0.20 mol.) in water (3 ml.) and ethanol (60 ml.) and the resulting mixture is refluxed for 1 hour on the steam bath with β-dimethylaminoethyl chloride hydrochloride (15.0 gm; 0.1 mol.). The mixture is then cooled, the precipitated potassium chloride is removed by filtration and the filtrate and washings are concentrated *in vacuo*. The residual oil is taken up in 2N hydrochloric acid (50 ml.) and unchanged dichlorophenol is extracted with ether. Excess solid potassium carbonate is added to the aqueous acid solution, the precipitated base is extracted with ether and the ethereal solution is dried with potassium carbonate. Dry hydrogen chloride is then passed in until the mixture is just permanently acid to Congo Red. The precipitated salt is filtered off and washed with ether to give 2-(β-dimethylaminoethoxy)-1:3-dichlorobenzene hydrochloride (11.2 gm.), m.p. 165—169° C. which, after recrystallisation from a mixture of alcohol, acetone and ether, melts at 169—170°C.

EXAMPLE II

Sodium (1.38 gm; 0.06 mol.) is dissolved in methanol, 2:6-dichlorophenol (9.9 gm; 0.06 mol.) is added, the solution is evaporated to dryness and the solid residue is dissolved in acetone (50 ml.). To a solution of β-diethylaminoethyl chloride hydrochloride (10.5 gm; 0.06 mol.) in water (6.0 ml.) is added first ether and then an excess of solid potassium carbonate (15 gm.) with cooling. The ethereal solution and ether rinsings are decanted from the stiff paste into the above acetone solution. The ether is then boiled off until the temperature of the reaction mixture is 55°C. and the mixture is then refluxed for 4 hours. The mixture is then cooled, the precipitated sodium chloride is removed by filtration and, proceeding as described in Example I, 2-(β-diethylaminoethoxy)-1:3-dichlorobenzene hydrochloride (14.5 gm.), m.p. 115—117°C., is obtained which, after recrystallisation from acetone-ether, melts at 117—118°C.

EXAMPLE III

Proceeding as described in Example II but commencing with sodium (3.45 gm; 0.15 mol.), 2:6-xylenol (18.3 gm; 0.15 mol.) and 3-dimethylamino-2-chloropropane hydrochloride (24 gm; 0.15 mol.) a crude hydrochloride (31 gm.) m.p. 146—170°C. is obtained from which 2-(2^1-dimethylamino-1^1-methylethoxy) 1:3-dimethylbenzene hydrochloride, m.p. 159—160°C. is obtained by fractional crystallisation from acetone.

EXAMPLE IV

Proceeding as described in Example II but commencing with sodium (2.8 gm; 0.122 mol.), 2:6-xylenol (16.5 gm; 0.135 mol.) and 3-diethylamino-2-chloropropane hydrochloride (22.4 gm; 0.12 mol.), a mixture of hydrochlorides (33 gm.), m.p. 110—149°C. is obtained which, on fractional crystallisation from acetone, yields 2-(2^1-diethylamino-2^1-methylethoxy)-1:3-dimethylbenzene hydrochloride (11.8 gm.), m.p. 161—162°C. and 2-(2^1-diethylamino-1^1-methylethoxy)-1:3-dimethylbenzene hydrochloride (12.6 gm.), m.p. 115—121°C. which, on crystallisation from a mixture of alcohol, acetone and ether, melts at 120—121°C.

EXAMPLE V

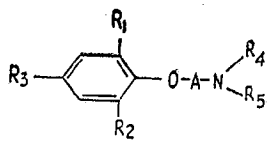
The following compounds can be prepared in manner similar to that described in any of the preceding Examples or by allowing the corresponding aryloxy ethyl bromide to react in a sealed ampoule at room temperature with an excess of an ethereal solution of dimethylamine or diethylamine.

(a) *β-(2:6-Xylyloxy)ethyldimethylamine.* Liquid, b.p. 124°C./10 mm. The hydrobromide crystallized from methanol in needles m.p. 166°C.

(b) *β-(2:6-Xylyloxy)ethyldiethylamine.* Liquid b.p. 131°C./10 mm. The hydrobromide crystallized from methanol in needles m.p. 151°C.

What we claim is:—

1. Aminoalkyl phenyl ethers of the formula:



in which R_1 and R_2 are the same or different and are chlorine atoms or lower alkyl groups and R_3 is a hydrogen atom or, where one or both of R_1 and R_2 are lower alkyl groups, a lower alkyl group, A represents a divalent group selected from

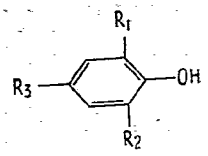
$$-CH_2-CH_2-,\quad -CH_2-CH_2-CH_2-,\quad -\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\quad\text{and}\quad CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-$$

and R_4 and R_5 each represent a lower alkyl group.

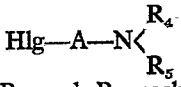
2. 2 - (β - Dimethylaminoethoxy) -1:3- dimethylbenzene.

3. 2 - (β - Diethylaminoethoxy) - 1:3 - dimethylbenzene.

4. A process for preparing the amino-alkyl phenyl ethers claimed in claim 1 which comprises reacting the corresponding phenol of the general formula:



(wherein R_1, R_2 and R_3 each have the significance hereinbefore set forth) with a dialkylaminoalkyl halide, preferably the chloride, of the general formula:



(wherein A, R_4 and R_5 each have the significance hereinbefore set forth and Hlg represents a halogen atom), in the presence of an acid binding agent.

5. Processes for preparing the aminoalkyl phenyl ethers claimed in claims 1, 2 and 3 when carried out substantially as described in the foregoing Examples.

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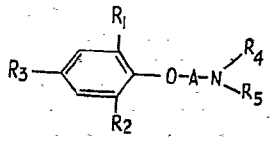
PROVISIONAL SPECIFICATION

Improvements in or relating to New Aminoalkyl Phenyl Ethers

We, THE UNIVERSITY OF LEEDS, a British Body Corporate, of University Road, Leeds, in the County of York, do hereby declare this invention to be described in the following statement:—

This invention relates to new aminoalkyl phenyl ethers and particularly to the production of such compounds which have valuable therapeutic activity.

According to the present invention there are provided new aminoalkyl phenyl ethers of the general formula I:—



... I

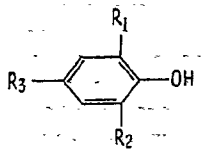
in which R_1, R_2 and R_3 are hydrogen atoms, halogen atoms, lower alkyl or lower alkoxy groups not more than one being hydrogen, A is a divalent group selected from

$$-CH_2-CH_2-,\quad -CH_2-CH_2-CH_2-,\quad -\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\quad\text{and}\quad -CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-$$

and R_4 and R_5 are lower alkyl groups. By the term "lower alkyl group" is meant alkyl groups containing up to 4 carbon atoms.

The said compounds are of therapeutic value and the preferred members of the class are potent local anæsthetics of prolonged duration of action and low toxicity.

According to a further feature of the invention, the compounds of general formula I are prepared by reacting a compound of the general formula II:—



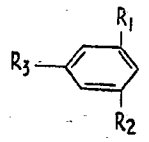
... II

with a compound of the general formula III:—

X—Y ... III

where X represents a reactive ester grouping, and with particular advantage a halogen atom, and Y represents a grouping of the structure —A—N$\langle^{R_4}_{R_5}$, or a grouping readily convertible thereto, e.g. —A—Br or —A^1CONH_2 (A^1 represents a grouping differing from A only in the omission of a terminal —CH_2— grouping).

More particularly the compounds of the present invention may be made by the foregoing and other related methods as follows. In the equations illustrating these methods the group:



is represented by Ar. The other symbols have the significance given above.

A. The compounds of general formula I may be prepared by

(i) the addition of the appropriate compound to a secondary amine, thus:

$$Ar—O—A—M + NHR_4R_5 \longrightarrow Ar—O—A—NR_4R_5$$

the reaction being carried out in the presence of a base such as pyridine or potassium carbonate.

(ii) by the reaction of the appropriate phenol with an appropriate ester, thus:

$$Ar—OH + M—A—NR_4R_5 \longrightarrow Ar—O—A—NR_4R_5$$

the reaction being carried out in the presence of a base, e.g. pyridine or dimethylaniline.

(iii) by reduction of a corresponding amide thus:

$$Ar—O—A^1—CONR_4R_5 \longrightarrow Ar—O—A—NR_4R_5$$

the reduction being preferably effected with hydrogen in the presence of catalysts or by reducing agents such as lithium aluminium hydride.

(iv) by the alkylation of the corresponding primary amines, thus:

$$Ar—O—A—NHR_4 + R_5M \longrightarrow Ar—O—A—NR_4R_5$$

the reduction being effected preferably in the presence of an organic or inorganic base.

B. The compounds of the type Ar—O—A—NHR_4 referred to in Section A(iv) above may be produced by either of the following methods:

(i) by reaction of the appropriate ester and phenol, thus:

$$Ar.OH + M—A—NHR_4 \longrightarrow Ar—O—A—NHR_4$$

preferably in the presence of an organic or inorganic base.

(ii) by reaction of the amine with a suitable alkyl ester, thus:

$$Ar—O—A—NH_2 + R_4X \longrightarrow Ar—O—A—NHR_4$$

preferably in the presence of an organic or inorganic base.

C. The compounds Ar—O—A—NH_2 referred to in Section B(ii) may be prepared by the following method:

(i) by reaction of the appropriate phenol and ester, thus:

$$Ar—OH + M—A—NH_2 \longrightarrow Ar—O—A—NH_2$$

preferably in the presence of an organic or inorganic base.

D. The compounds of the formula Ar—O—A—M referred to in Section A(i) above may be prepared by the following method:

(i) by reaction of the appropriate phenol with an appropriate diester, thus:

$$Ar—OH + M—A—M \longrightarrow Ar—O—A—M$$

preferably in the presence of an organic or inorganic base.

E. The compounds of the formula

$$Ar—O—A^1—CONR_4R_5$$

referred to in section A(iii) above may be prepared by the following method:—

$$Ar—OH + M—A^1—CO—NR_4R_5 \longrightarrow Ar—O—A^1—CONR_4R_5$$

The groups R_1, R_2 and R_3 of the Ar nucleus may be introduced at any convenient stage in the course of the synthesis set forth above.

The preferred compounds according to the present invention are 2-(β-dimethylaminoethoxy) 1:3-dimethylbenzene and the corresponding diethylamino compound.

The following Examples will serve to illustrate the production of compounds of the formula Ar—O—A—M (above):—

EXAMPLE I

2:6-Xylenol (24.4 gm; 0.2 Mol.) is dissolved in 1:2-dibromoethane (112 gm; 0.6 Mol.) and ethanol (100 ml.). The mixture is heated to reflux and stirred, and a solution of sodium hydroxide (12 gm; 0.3 Mol.) in water is added during 3 hours and heating and stirring continued for a further 12 hours. Dilution of the reaction mixture with water permits the separation of an organic layer which, on distillation, yields about 30 gm of β-(2:6-xylyloxy)-ethyl bromide b.pt. 138—139°C. at 16 mm. pressure, which is a colourless liquid having $[n]_D^{20°}$ 1.5391.

EXAMPLE II

2:4:6-Mesitol (20.4 gm; 0.15 Mol.) is dissolved in 1:2-dibromo-ethane (84 gm; 0.45 Mol.) and heated to 100°C. with reflux and mechanical stirring. Potassium hydroxide (17 gm; 0.3 Mol.) dissolved in methanol (80 ml.) is added during six hours and heating and stirring continued for a further 48 hours. Dilution of the reaction product with water permits the separation of an organic layer which, on distillation, yields about 15 gm. of β-(2:4:6-mesityloxy)ethyl bromide which is a colourless liquid of b.pt. 148°C. at 15 mm. pressure and has $[n]_D20°$ 1.5348.

For the Applicants
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